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Regulation of the specific DNA binding function of p53.

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The DNA binding activity of p53 is required for its tumor suppressor function; we show here that this activity is cryptic but can be activated by cellular factors acting on a C-terminal regulatory domain of p53. A gel mobility shift assay demonstrated that recombinant wild-type human p53 binds DNA sequence specifically only weakly, but a monoclonal antibody binding near the C terminus activated the cryptic DNA binding activity stoichiometrically. p53 DNA binding could be activated by a C-terminal deletion of p53, mild proteolysis of full-length p53, E. coli dnaK (which disrupts protein-protein complexes), or casein kinase II (and coincident phosphorylation of a C-terminal site on p53). Activation of p53 DNA binding may be critical in regulation of its ability to arrest cell growth and thus its tumor suppressor function.

PMID: 1423635, UI: 93046690

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Identification of an additional negative regulatory region for p53 sequence-specific DNA binding.

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The DNA binding activity of p53 is crucial for its tumor suppressor function and is subject to tight regulation. Previous studies revealed that the inhibitory function of the p53 C terminus is implicated in the latent, low affinity sequence-specific DNA binding activity of p53 in the uninduced state. Sequence-specific DNA binding of p53 has been shown to be activated by several posttranslational modifications and interacting proteins that target predominantly the C terminus. Moreover, several authors have shown that synthetic peptides corresponding to p53 C-terminal sequences activate p53 sequence-specific DNA binding. In an effort to identify the interaction site of p53 with these activating peptides we assessed complex formation between p53 deletion constructs and C-terminal activating peptides by peptide affinity precipitation. This study revealed that two distal regions of the p53 molecule contribute synergistically to the interaction with activating C-terminal peptides: amino acids 80-93 and 364-393. The C-terminal residues 364-393 are already well characterized as having negative regulatory function. DNA binding analyses with these deletion constructs reveal a comparable negative regulatory activity for residues 80-93, defining this region as a previously unidentified negative regulatory domain of p53. Furthermore, synthetic peptides spanning this newly identified proline-rich negative regulatory region (residues 80-93) are able to activate p53 sequence-specific DNA binding in vitro. We suggest that both negative regulatory regions, residues 80-93 and 364-393, contribute cooperatively to the maintenance of the latent, low-affinity DNA binding conformation of p53.

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Regulation of p53 protein function through alterations in protein-folding pathways.

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The tumour suppressor protein p53 is a stress-activated transcription factor whose activity is required for regulating the cellular response to stress and damage. The biochemical activity of p53 as a transcription factor can be regulated by partner proteins affecting stability, nuclear transport, signalling pathways modulating phosphorylation and interactions with components of the transcriptional machinery. The key structural determinants of p53 protein that drive sequence-specific DNA binding include the core specific DNA-binding domain and the tetramerization domain. Flanking these domains are more evolutionarily divergent carboxy- and amino-terminal regulatory motifs that further modulate tetramerization and sequence-specific transactivation. This review will mainly focus on the mechanisms whereby the tetramerization domain modulates sequence-specific DNA binding and how missense point mutations in p53 protein and the activity of molecular chaperones may lead to unfolding of mutant p53 tetramers in human tumours.

Publication Types:

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Wild-type p53 adopts a 'mutant'-like conformation when bound to DNA.

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p53 is a negative regulator of cell growth. The majority of human tumors express mutant p53 proteins, which can be distinguished from wild-type by their immuno-reactivity to a panel of conformation-specific monoclonal antibodies, such as PAb421, PAb1620 and PAb246. Wild-type p53 has sequence-specific DNA binding activity. We demonstrate that upon binding DNA wild-type p53 changes conformation at both its N- and C-termini, such that it adopts a 'mutant'-like conformation. Very few of the known DNA binding proteins exhibit long-range conformational changes upon binding to DNA. Such proteins, like the Drosophila heat shock transcription factor, have DNA binding domains whose activity is regulated by conformation. The DNA binding activity, and therefore the function, of wild-type p53 may be regulated via its ability to adopt distinct conformations.

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